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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,950	04/08/2005	Jean-Pierre Fryns	50304/078001	4493
21559	7590	10/22/2007		
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			EXAMINER GREENE, JAIME M	
			ART UNIT 1634	PAPER NUMBER
			NOTIFICATION DATE 10/22/2007	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

<b>Office Action Summary</b>	Application No. 10/530,950	Applicant(s) FRYNS ET AL.	
	Examiner Jaime M. Greene	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 August 2007.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 63-95 is/are pending in the application.
- 4a) Of the above claim(s) 69,70,74 and 76-95 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 63-68, 71-73, and 75 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some    \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>8/07, 7/05</u> | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u>                   |

### **DETAILED ACTION**

1. This action is in response to papers filed 8/3/07. Claims 63-95 are pending, and claims 63-68, 71-73, and 75 are under examination on the merits.

#### ***Information Disclosure Statement***

2. The information disclosure statements (IDS) were filed on 8/3/07 and 7/25/05. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

#### ***Sequence Compliance***

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. There are no sequence identifiers for the sequences listed throughout the specification and there is no corresponding computer readable format. Applicant is required to thoroughly review the specification and comply with all sequence rules. For example, the following sequences in the specification do not have sequence identifiers: the nucleic acid sequences on page 53. For any response to this office action to fully responsive, applicants are required to comply with sequence rules.

#### ***Election/Restrictions***

4. Applicant's election without traverse of Group I, claims 66-68 and 75, which includes linking claims 63-65 and 71-73 in the reply filed on 8/3/07 is acknowledged.

5. Claims 68-70, 74, and 76-95 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/3/07.

### ***Claim Objections***

6. Claim 64 is objected to because of the following informalities: The claim does not end in a period. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 63-68, 71-73, and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 63-68, 71-73, and 75 are broadly drawn to a method for testing or screening a mammal thought to have or be predisposed to a neural system disorder comprising detecting the presence of any mutation in the NBEA gene or its associated

promoter in a sample of said mammal. The claims encompass examining any mutation/polymorphism in any animal NBEA gene.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification teaches GenBank Accession number 22052081. However, the specification does not provide any sequences that further define the human NBEA gene or its promoter or the gene or promoter for any other mammals. Regarding mutations, the specification teaches two probes used to detect a breakpoint in the NBEA gene. However, the specification does not specifically identify the location of or the sequence of the breakpoint. The specification does not provide further examples of mutations in any mammalian NBEA genes. . In addition, the GeneCard for human the NBEA gene (<http://genecards.org/cgi-bin/carddisp.pl?gene=NBEA&search=nbea>, Last full update: 21 Aug 2007) teaches that there are 2002 known SNPs/mutations in the NBEA gene, however none of these mutations were described at the time the invention was made.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics ( i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification teaches that the mutations can include a modification selected from a substitution, a deletion, a frame-shift, an insertion, or an altered epigenetic control. However, the specification does not provide any examples of said modifications. . In addition, the GeneCard for

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human the NBEA gene ((<http://genecards.org/cgi-bin/carddisp.pl?gene=NBEA&search=nbea>, Last full update: 21 Aug 2007) teaches that there are 2002 known SNPs/mutations in the NBEA gene, however none of these mutations were described at the time the invention was made.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Also, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.)

In the instant application, with the exception of the GenBank accession number and the two probes, one of skill in the art cannot envision the detailed chemical structure of in the NBEA gene or its associated promoter in humans or any other mammals.

Finally, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a

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DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

Id. at 1170, 25 USPQ2d at 1606.

The limited information provided regarding the sequence of the NBEA gene in humans is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for testing or screening a mammal thought to have or be predisposed to a neural system disorder comprising detecting the presence of a mutation in the NBEA gene or its associated promoter in a sample of said mammal.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for claims 63-68, 71-73 and 75.

### ***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 63-68, 71-73 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.



The breadth of the claims and nature of the invention

Claims 63-68, 71-73 and 75 are broadly drawn to a method for testing or screening a mammal thought to have or be predisposed to a neural system disorder comprising detecting the presence of a mutation in the NBEA gene or its associated promoter in a sample of said mammal. The claims encompass examining any mutation/polymorphism in any animal NBEA gene and using that mutation for testing or screening a mammal.

The nature of the invention involves using any mutation in the NBEA gene or promoter and correlating that mutation with any neural system disorder.

Guidance in the Specification and Working Examples

The specification teaches a molecular genetic analysis of an autistic male (page 41, line 26). The specification teaches identifying a breakpoint in the neurobeachin gene in said patient. The specification does not provide any additional studies correlating NBEA with a neural system disorder in human or in any other mammals. Also, the specification does not define what disorders are encompassed by neural system disorders.

The unpredictability of the art, the state of the prior art, level of skill in the art

While the state of the art and level of skill in the art with regard correlating gene expression with disease detection and diagnosis is high, the level of unpredictability in associating any one gene expression level with disease progression is even higher.

The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

A search for neural system disorder did not yield any results, suggesting that it is not an art recognized term to define a particular category of diseases. However, the term "neural" is defined by the Merrium-Webster Online dictionary (Merrium-Webster Online dictionary. Definition for "Neural". Copyright 2006-2007, Merrium-Webster Inc. URL: <http://www.m-w.com/dictionary/Neural>) as "of, relating to, or affecting a nerve or the nervous system". Therefore, the claims broadly encompass any disease or disorder or the nervous system including neuroblastoma, Alzheimer's disease, schizophrenia, etc. Also, regarding the reference to disorders associated with brain anomalies in claim 72, the Merck Manual teaches brain anomalies, and identifies these as congenital anomalies. The Merck manual further identifies several brain anomalies including Hydrocephalus, Anencephaly, Encephalocele, Malformed cerebral hemispheres, Porencephaly, Septo-optic dysplasia, all of which are associated with at least one of the symptoms in claim 72 (such as disturbed cognitive function or disturbed motor control), and therefore also encompassed by neural system disorders.

Regarding applying polymorphisms identified in one disease to other diseases Möller (Möller, et al. Neuroscience Letters, 15 April 2004; 359(3):195-197.) teaches that although several studies have established IL-1 $\alpha$  as a risk factor for Alzheimer's disease, this seems not to be true in patients suffering from Parkinson's disease. Therefore, is it unpredictable to use research on polymorphisms in one disorder and directly apply them to other disorders without unpredictable experimentation.

Regarding polymorphisms in the NBEA gene, the GeneCard for NBEA (<http://genecards.org/cgi-bin/carddisp.pl?gene=NBEA&search=nbea>, Last full update:

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21 Aug 2007) teaches that there are 2002 known SNPs/variants in the human NBEA gene. The GeneCard also teaches 3 known mammalian orthologs for the human gene, namely in dog, chimpanzee, and mouse. In addition, the MGI entry for the mouse NBEA gene (MGI entry for the mouse NBEA gene; URL <http://www.informatics.jax.org/javawi2/servlet/WIFetch?page=markerDetail&key=43458>, last update 10/10/2007) teaches that there are 811 known polymorphisms in the mouse gene. Regarding NBEA and autism, Castermans (Castermans et al. J Med Genet.2003; 40: 352-356) teaches that the neurobeachin gene is disrupted by a translocation in a patient with idiopathic autism. There were no other NBEA mutations in the art that are correlated with any of the disorders described in the claims, specification or falling into the category of brain anomalies described above.

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied before the broad scope of the claims could be practiced without undue and unpredictable experimentation.

The claims are broadly drawn to a method for testing or screening a mammal thought to have or be predisposed to a neural system disorder comprising detecting the presence of any mutation in the NBEA gene or its associated promoter. The specification does not specify which diseases are encompassed by a neural system disorder. The Merriam-Webster Online dictionary teaches that the definition of neural is "of, relating to, or affecting a nerve or the nervous system". Therefore, the claim broadly

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encompasses any disease or disorder associated with the nervous system. The specification also teaches identifying a breakpoint in the neurobeachin (NBEA) gene in an autistic patient. However, Möller teaches that a polymorphism associated with Alzheimer's disease (i.e. a neural system disorder) is not associated with Parkinson's disease (i.e. another neural system disorder). This suggests that not all neural disorders have the same mechanisms and associations with polymorphisms/mutations. Therefore, the skilled artisan would be required to analyze polymorphisms in the NBEA gene for each neural system disorder in order to determine which polymorphisms can be associated with each disorder. This would require undue experimentation with no expectation of success.

The claims are broadly drawn to a method for testing or screening a mammal thought to have or be predisposed to a neural system disorder comprising detecting the presence of any mutation in the NBEA gene. The specification does not specifically identify any polymorphisms. The GeneCard for the human NBEA gene teaches that there are 2002 polymorphisms/mutations known in the NBEA gene. The MGI entry for the mouse NBEA gene teaches that there are 811 known polymorphisms in the mouse gene. Therefore, the skilled artisan would be required to perform a large study to determine which of the multitude of polymorphism can be associated not only with autism but also with all neural system disorders. The skilled artisan would be required to do this not only for the 2002 human polymorphisms but also for the 811 mouse polymorphisms and the unknown other numbers of polymorphisms in other mammals.

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This would require undue and unpredictable experimentation with no expectation of success.

### Conclusion

Given the lack of data regarding polymorphisms in the NBEA gene and their disease associations along with the large number of known polymorphisms and the broad interpretation of neural system disorder based on the information in the specification, a method for testing or screening a mammal thought to have or be predisposed to a neural system disorder comprising detecting the presence of a mutation in the NBEA gene or its associated promoter in a sample of said mammal. Is replete with unpredictable experimentation that is considered undue.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the methods of the claims as broadly written.

### ***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claim 63 is rejected under 35 U.S.C. 102(b) as being anticipated by RefSNP# rs374452, Assay ID ss478228 (RefSNP# rs374452 Assay ID ss478228 Entry date 07/12/00, URL

[http://www.ncbi.nlm.nih.gov/SNP/snp\\_ref.cgi?searchType=adhoc\\_search&type=rs&rs=rs374452](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs374452); method described at URL:

[http://www.ncbi.nlm.nih.gov/SNP/snp\\_viewTable.cgi?mid=559](http://www.ncbi.nlm.nih.gov/SNP/snp_viewTable.cgi?mid=559)).

The NCBI dbSNP database teaches rs374452, assay ss478228, a polymorphism in the Human NBEA gene. The entry for notes that the polymorphism was for human, and the information regarding Assay ID ss478228 teaches that the method for detecting the polymorphism was as follows: "Clone overlaps from available finished and unfinished public human genomic sequence were aligned and high quality base discrepancies ( $Q \geq 23$ ) were identified as candidate SNPs".

Therefore all limitations of claim 63 are taught by the reference.

### ***Claim Rejections - 35 USC § 103***

12. Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over RefSNP# rs374452, Assay ID ss478228 (NCBI dbSNP database RefSNP# rs374452 Assay ID ss478228 Entry date 07/12/00, URL [http://www.ncbi.nlm.nih.gov/SNP/snp\\_ref.cgi?searchType=adhoc\\_search&type=rs&rs=rs374452](http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs374452); method described at URL: [http://www.ncbi.nlm.nih.gov/SNP/snp\\_viewTable.cgi?mid=559](http://www.ncbi.nlm.nih.gov/SNP/snp_viewTable.cgi?mid=559)) in view of Arnold (Arnold, et al. US Patent Number 6410231, Granted 6/25/02).

Note that the NCBI dbSNP database RefSNP# rs374452 entry and the corresponding method are considered a single reference

The NCBI dbSNP database teaches rs374452, assay ss478228, a polymorphism in the Human NBEA gene. The entry for notes that the polymorphism was for human, and the information regarding Assay ID ss478228 teaches that the method for detecting the polymorphism was as follows: "Clone overlaps from available finished and unfinished public human genomic sequence were aligned and high quality base discrepancies ( $Q \geq 23$ ) were identified as candidate SNPs"

The NCBI dbSNP database entry for rs374452, assay ss478228 does not teach detecting the mutation by hybridization with a labeled probe. However Arnold teaches a method for detecting SNPs by hybridization of a SNP probe to its corresponding SNP (claim 1). Arnold teaches that each SNP probe comprises a label (claim 6). Arnold also teaches that the method can detect multiple SNPs in a population of target polynucleotides (claim 1).

Therefore, it would have been prima facie obvious one of ordinary skill in the art at the time the invention was made to detect the SNP rs374452, assay ss478228 by using a labeled SNP probe in order to detect multiple SNPs in a population of target polynucleotides.

One of ordinary skill in the art would be motivated to detect the SNP rs374452, assay ss478228 by using a labeled SNP probe as part of a method to detect multiple SNPs in a population of target polynucleotides.

There is a reasonable expectation of success because Arnold is a common method in the art for SNP detection.

**Conclusion**


None of the claims have been allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jaime M. Greene whose telephone number is 571-270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jaime Meredith Greene 10/11/07

  
JEANINE A. GOLDBERG  
PRIMARY EXAMINER  
10/15/07



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<b>Notice to Comply</b>	Application No. <b>10530950</b>	Applicant(s) <b>Eryns, et al.</b>
	Examiner <b>Greene</b>	Art Unit <b>1634</b>

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

**Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-0731 or (571) 272-0951  
 For CRF Submission Help, call (571) 272-2510  
 PatentIn Software Program Support  
 Technical Assistance. 1-866-217-9197 or 703-305-3028 or 571-272-6845  
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